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Beyond the bleed: complications after aneurysmal subarachnoid hemorrhage. Pathophysiology, clinical implications, and management strategies: a review

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Abstract

Aneurysmal subarachnoid hemorrhage is a critical condition with high case-fatality and lasting impacts on survivors. Acute events that are the direct result of aneurysm rupture, such as acute ischemia, elevated intracranial pressure, cerebral edema, seizures, and hydrocephalus, lead to early brain injury. A delayed cascade of processes, including a prominent systemic inflammatory response, may lead to secondary brain injury and delayed cerebral ischemia, which often further impairs recovery. Systemic complications, including cardiac and pulmonary dysfunction, fever, and electrolyte imbalances, arise in the interplay between early and secondary brain injury and challenge the clinical course. Early management focuses on the prevention of rebleeding mainly through aneurysm securement, amelioration of early brain injury through cerebrospinal fluid drainage, control of intracranial pressure, and organ support to avoid or attenuate secondary brain injury. Nimodipine remains the only pharmacological agent shown to reduce delayed cerebral ischemia, and lumbar drainage of cerebrospinal fluid to reduce subarachnoid blood may improve outcome. Management strategies for hemodynamic interventions, seizures, intracranial pressure control, large artery vasospasm, and electrolytes remain consensus-based and with large variation in practice. Several advances in understanding inflammation and delayed cerebral ischemia, as well as in monitoring and interventions hold promise, but robust trials are needed to refine protocols and improve patient recovery. Understanding and mitigating the cascade of damage from rupture to recovery is essential to reduce the burden of this devastating condition. In this review, we appraise the current understanding of the pathophysiology of post-rupture complications as well as scientific and management data, with a focus on recent advances.

Keywords Subarachnoid hemorrhage, Aneurysmal subarachnoid hemorrhage, Brain ischemia, Cerebral infarction, Vasospasm, Intracranial, Brain injuries

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Introduction

Subarachnoid hemorrhage from the rupture of an intracranial aneurysm (aSAH) carries a 30-day mortality of ~ 40% [1–3]. Many survivors suffer from long-term deficits [4]. During an aneurysm rupture, blood pours into the subarachnoid space at arterial pressure, with subsequent potential for acute cerebral ischemia, elevated intracranial pressure, cerebral edema, seizures, and hydrocephalus, often severely impairing cerebral perfusion. This cerebral hypoperfusion—constituting the early attack on the brain, as well as the toxic effects of blood in the cerebrospinal fluid (CSF), further lead to an array of disturbances, including the metabolic crisis in neurons, blood–brain barrier breakdown, cytotoxic and vasogenic edema, electrochemical discharges (cortical spreading depolarizations, CSD oxidative stress, which exacerbate [5]), impaired drainage of solutes through the glymphatic and lymphatic system, and activation of inflammatory pathways [6, 7]. Events occurring within 72 h of an aneurysm rupture that lead to brain damage are often referred to as "early brain injury" (EBI) [8]. EBI further initiates a cascade of events, which may be associated with delayed cerebral ischemia (DCI) [9–11]. EBI also impacts systemic function, mediated by a stress response. Understanding the early reaction of the body to aneurysm rupture may be key to preventing progression to the cascade of injury downstream from the ictus.

In this review, we provide an updated appraisal on the pathophysiology of early and late complications as well as a critical review of the current and future approaches to their management, including ongoing scientific efforts and new findings since the iteration of the most recent management guidelines [12, 13] on the topic in 2023.

Role of early pathophysiological events and inflammation in the pathogenesis of post-rupture complications

After aSAH, global ischemia and accumulation of toxic blood breakdown products promote the development of EBI, characterized by a series of secondary pathophysiological downstream events, including alteration of ionic homeostasis, microvascular dysfunction, blood brain barrier (BBB) breakdown, cerebral edema, neuroinflammation, and oxidative stress, which exacerbate brain damage [8]. Microvascular dysfunction after aSAH involves endothelial cell swelling, loss of tight junction integrity, pericyte degeneration, and microthrombi formation, all contributing to impaired autoregulation and heterogeneous perfusion at the capillary level [14]. Experimental studies show that endothelial nitric oxide synthase plays a protective role in maintaining microvascular integrity in EBI, while early BBB breakdown has been linked to poor clinical outcomes [15–17]. Metabolic dysregulation during EBI, including mitochondrial dysfunction and energy failure, represents another potential therapeutic target [18, 19]. It has been demonstrated in animal models that real-time metabolic monitoring revealed early energetic collapse within the first hours following hemorrhage [18], and that preserving mitochondrial homeostasis reduces neuronal apoptosis and improves neurological outcomes after aSAH [19]. There is substantial evidence that inflammation is a driver of many of the complications associated with aSAH [7]. First, inflammation of the aneurysm wall with a collection of macrophages accumulating on the aneurysm dome probably predisposes to rupture, with a likely role of matrix metalloproteinase-9 in the rupture event. Innate inflammatory cells—monocytes and neutrophils—in the periphery, and microglia and astrocytes in the central nervous system, are activated early after rupture [20–22]. A lymphocytic response of adaptive T-lymphocytes, B-lymphocytes, natural killer cells (NK), and NK-T-cells in aneurysm rupture increases neuroinflammatory signaling, reinforcing the recruitment and activation of additional immune cells, resulting in a maladaptive and self-propagating process [23, 24]. Observational studies have shown that subsets of CD4 + T-cells display dynamic changes in peripheral blood and CSF of aSAH patients, suggesting a role in disease progression [25–27]. Moreover, promoting lymphatic clearance of pro-inflammatory Th17 cells has shown therapeutic promise in experimental models [28, 29]. However, a substantial knowledge gap persists in understanding the specific contribution of lymphocytic responses following aSAH. The current understanding of separate innate and adaptive immune responses described in infection appears to be less applicable to 'sterile' injuries such as aSAH [30]. Bone-marrow-derived inflammatory cells, as well as brain resident immune cells, and inflammatory system elements all play a role in the development of DCI and the evolution of brain damage[30]. A critical question that underlies the treatment or prevention of DCI is what part of the inflammatory system initiates the cascade. Finding early initiators may hold the best chance for effective treatments.

Delayed Cerebral Ischemia (DCI)

DCI, defined as lasting focal neurological impairment or decrease of ≥ 2 points on the Glasgow Coma Scale that was not apparent immediately after aneurysm occlusion and is not attributable to other causes [11], affects 20–30% of patients, mostly between days 4–14, and is a main risk factor for poor outcomes [31]. The pathogenesis of DCI is complex. While initially assumed to be caused by large artery vasospasm, this concept has been replaced by a multifactorial model involving both macro- and microenvironmental derangements where DCI is the result of various processes resulting in a mismatch between perfusion and metabolism, including microvascular and macrovascular vasospasm, inflammation and

activation of the innate immune system [7, 32], CSD, impaired autoregulation with reduced regional blood flow, intravascular volume contraction, and microthrombosis. CSD, waves of near-complete neuronal and glial depolarization that propagate slowly through the cortex, have been identified for nearly two decades as a factor in the progression to secondary brain injury. Occurring in the setting of disturbed autoregulation [33], CSD can lead to a mismatch between metabolic demand and cerebral blood flow, triggering vasoconstriction, neuroinflammation, and microthrombotic cascades. Notably, repetitive or clustered CSDs can worsen ischemic injury by extending zones of hypoperfusion and perpetuating a harmful cycle of excitotoxicity and inflammation [34, 35].

Microthrombosis is another increasingly recognized contributor to DCI, with activation of platelet and coagulation cascade leading to diffuse microvascular obstruction, especially in the setting of neuroinflammation sustained by persistent activation of microglia and astrocytes [36, 37]. These microthrombi typically remain undetected on conventional angiography but are responsible for diffusion hypoxia, thus contributing to a significant reduction in tissue perfusion, further compounding ischemic risk. Microcirculatory impairment, which may arise from endothelial injury, pericyte dysfunction, capillary constriction, and leukocyte plugging, plays a pivotal role in perfusion–metabolism mismatch. Some studies have indicated that cerebral circulation time can reflect the status of microcirculatory impairment, with its increase correlating with the occurrence of DCI and poor outcome, independent of macrovascular vasospasm. This suggests that greater microcirculatory dysfunction from the ultra-early phase to the subacute phase can be a causative factor for DCI development and poor outcome [38] Non-modifiable factors predicting DCI include poor initial clinical grade and more subarachnoid blood [39], as well as—less consistently—female sex, smoking, hydrocephalus, hyperglycemia, and diabetes [40].

The goal of treating DCI is to halt the process(es) impairing brain perfusion and minimize progression to infarction. At present, the only data-proven strategy to reduce the occurrence of DCI is enteral nimodipine. Additionally, accepted means to reduce DCI include avoidance of hypovolemia and hypotension [12]. Removal of CSF has emerged as a preventive measure to lessen DCI and decrease the rate of unfavorable outcomes, although trial results have not been consistent [41–43].

A major challenge in interpreting currently available data is that, despite the attempt to unify the definition of DCI and adopt it as a common data element in aSAH research [44], there is no accurate diagnostic tool, rendering detection and monitoring difficult, especially in comatose or sedated patients (see Table 1). While treatment based on advanced multimodal monitoring, for example, through brain oxygenation protocols [45–47] has shown promising results to mitigate secondary brain injury in select settings, clear evidence on its efficacy on outcomes is lacking, and RCT data are warranted. Wide variations in the definition and diagnosis of DCI prevail even in specialized centers [48]. Furthermore, the current definition may be too narrow for studies investigating the efficacy of strategies to reverse DCI upon occurrence, in which DCI reflects an entry event rather than an outcome [11].

Enteral nimodipine remains the only medication for which a reduction of DCI and poor functional outcome is supported by cumulative data from randomized controlled trials [67]. As nimodipine does not directly treat large vessel vasospasm, a dilatory effect on smaller arteries with the restoration of cerebral blood flow [68] may mediate the beneficial effect. Administration of enteral nimodipine is endorsed by guidelines [12, 13], but in practice often limited by the occurrence of systemic hypotension necessitating dose reduction or discontinuation [69]. Nimodipine is also available as an intravenous formulation, and while no dedicated efficacy data are available for this route, preliminary data indicate safety [70] and potentially equal efficacy for intravenous administration [71]. Intraarterial nimodipine may portend success in ameliorating refractory vasospasm, but continuous administration comes with significant side effects (e.g., hypotension, heparin-induced thrombocytopenia) [72], and data are skewed towards refractory vasospasm without robust data on the reduction of DCI. Incentivized by the issue of systemic hypotension, local administration of calcium channel blockers has been a focus of study. While intrathecal administration of nimodipine-particle did not substantiate, a recent phase 2b RCT examining the safety and preliminary efficacy of nicardipine-release-implants, inserted during aneurysm clipping to the Circle of Willis, found a near threefold reduction in the occurrence of moderate-to-severe vasospasm without safety concerns, rendering a phase 3 trial powered to assess outcomes indicated [73].

Intracranial complications

Rebleeding

The rebleeding risk for ruptured, unsecured aneurysms is around 12%; most rebleeding occurs within 24 h [74]—acknowledging heterogeneity in the timing of aneurysm securement and definition of rebleeding. Elevated systolic blood pressure (SBP), particularly above 160 mmHg [74], poorer clinical (i.e., higher World Federation of Neurosurgical Societies (WFNS) and Hunt-Hess grades) and radiological grades, and aneurysm characteristics are associated with a higher risk [75, 76]. Aneurysm securement within 24 h is the best strategy to mitigate rebleeding risk; however, ultra-early securement—within

Table 1 Modalities of detection and monitoring of delayed cerebral ischemia (DCI)

	Advantages	Disadvantages
Clinical exam	Universally available	DCI-related neurologic changes are missed in one-fifth, especially poor-grade, comatose patients [49] Sleep disruption (may contribute to secondary brain injury) [50]
Digital Subtraction Angiography	Gold standard to diagnose large-vessel vasospasm Ability to treat endovascularly	Invasive Focuses on large vessel spasm and not DCI
Computed tomography-angiography	82% and 97% sensitivity and specificity for vasospasm detection [50–52]	Radiation & Contrast Focuses on large vessel spasm and not DCI
Perfusion computed tomography	May detect impaired perfusion even in absence or independent of vasospasm [53]	no standardized methods for measuring perfusion with CTP after aSAH [54]
Transcranial Doppler Ultrasonography	non-invasive can be done repeatedly at the bedside	Variable sensitivity for vasospasm detection, reaching only 38% in a recent review [55] operator-dependent subject to confounders may trigger interventions aimed at vasospasm for DCI of different etiology [56]
Continuous quantitative electroencephalography (cEEG)	EEG changes correlative to decreased cerebral function include loss of background fast activity and increased slow activity with appearance of epileptiform abnormalities can indicate development of vasospasm and DCI earlier than TCD [57] metrics (alpha power, relative alpha variability, and alpha/delta ratio) have demonstrated value in identifying DCI [58–61]	Broad implementation challenging & and resource-intensive EEG carries poor signal-to-noise ratio predictive accuracy for DCI better when combined with TCD [62]
Invasive multimodal monitoring modalities	Includes various modalities: cerebral oxygenation [63], brain-tissue biochemistry, electrocorticography May be useful for select patients	Available data are limited in quality and preclude generalizability [64] Protocols aimed at optimizing brain oxygenation and cerebral metabolism suggest implementation of different strategies including increasing FiO2, temperature management, optimization of hemoglobin, optimization of flow through manipulation of cerebral perfusion pressure and carbon dioxide, as well as titration of analgesia and sedation
Vital sign trends	Advanced analytics may portend a future, broadly available, and low-cost way to discover DCI [65, 66]	Further studies necessary Not broadly available

DCI, Delayed Cerebral Ischemia; CTP, Computed-Tomography-Perfusion; EEG, Electroencephalography; TCD, Transcranial Doppler; FiO2, Inspired fraction of oxygen;

6 h—does not seem to add additional benefits and comes at the cost of a considerably higher burden on resources [77, 78]. Of note, no high-quality data are available for the use of newer embolization devices, which are increasingly used for ruptured aneurysms not readily amenable to traditional securement through coiling or clipping [79].

Rapidly and broadly modifiable factors to reduce rebleeding risk before aneurysm securement include blood pressure control and reversal of coagulopathy; for, neither exists strong data to support the impact of specific strategies. For blood pressure control, retrospective observations suggest that the risk of rebleeding is higher for cohorts with SBP > 160 mmHg [75]; retrospective data also indicate that lowering blood pressure decreases rebleeding risk, but may increase the risk of cerebral hypoperfusion and cerebral ischemia leading to EBI [80]. Greater blood pressure variability is associated with worse outcomes [81]. Existing data are flawed by methodological concerns and a high risk of bias [74]. In the absence of high-quality data which effectively mitigates the risk of bias, guidelines abandoned the provision of specific blood pressure targets and rather stated that treating severe hypertension on admission is reasonable, while sudden profound blood pressure reduction should be avoided [12, 13]. In practice, wide variability in management reflects the absence of known specific targets; SBP limits of 140 or 160 mmHg are frequently chosen [82].

Emergent reversal of coagulopathy in patients taking anticoagulants is strongly recommended [13], even if this recommendation is based on extrapolation of data for intracerebral hemorrhage without dedicated data on aSAH [83]. Antifibrinolytic drugs, such as tranexamic acid or aminocaproic acid, might decrease rebleeding risk by stabilizing the blood clot that seals the ruptured aneurysm. However, in the recent ULtra-early TRanexamic Acid after subarachnoid Hemorrhage (ULTRA [84]) trial, short-term (< 24 h) treatment with tranexamic acid did not reduce the risk of poor functional outcome [85].

Post-hoc analyses also found no benefit of tranexamic acid in subgroups of patients based on sex or clinical condition on admission [85]. In addition, the time interval between ictus and the start of tranexamic acid treatment had no impact on functional outcomes [86]. Therefore, the most recent guidelines [12, 13] recommend against the routine use of tranexamic acid.

High intracranial pressure

Elevated intracranial pressure (ICP) significantly influences outcomes [87–89]. Prolonged elevation of ICP and higher cumulative ICP burden, i.e. the sum of duration and intensity of ICP elevations rather than isolated thresholds, impairs cerebral oxygenation not only by reducing cerebral perfusion pressure but also by compressing microvasculature, disrupting venous outflow, and impairing oxygen diffusion and utilization at the tissue level and increases the risk of cerebral infarction, in-hospital mortality, and unfavorable long-term outcomes [90, 91]. Even moderate ICP burden at thresholds of 20- and 30-mm Hg increases mortality and correlates with worse outcomes [92]. ICP monitoring and related management, including escalation of therapeutic intensity, were associated with improved outcomes in the SYNAPSE-ICU study [88], and highlight the need for a more nuanced understanding of the cumulative ICP burden. While these findings may imply that early and targeted intervention to control ICP may affect recovery, an approach distinguishing whether ICP is a consequence of evolving underlying brain injury that may largely be irreversible, versus reflecting a secondary complication that is amenable to treatment, is yet to be investigated.

Disturbance of CSF circulation

Subarachnoid hemorrhage can disrupt cerebrospinal fluid dynamics by provoking inflammatory cascades and fibrin deposition that impair arachnoid granulation function—leading to a deficit in CSF reabsorption (communicating hydrocephalus)—and by inducing intraventricular adhesions that obstruct CSF pathways (non-communicating hydrocephalus). CSF drainage is a logical approach for controlling hydrocephalus and removing blood from the subarachnoid space. CSF can be drained through an external ventricular drain (EVD) placed into the lateral ventricle, an external lumbar drain (LD), or one or more lumbar punctures. Institutional practices to manage EVDs, both in relation to the adjustment of drainage in relation to ICP or other symptoms, as well as for weaning, vary widely and have not been systematically compared or investigated [93, 94]. A higher amount of CSF drained by EVDs may be associated with a worse outcome, even after adjusting for baseline hemorrhage severity [95]. Available, largely observational data indicate a potential advantage in rapid weaning strategies [96].

In the absence of obstructive hydrocephalus, CSF drainage via lumbar drain (LD) has also been proposed to remove blood from basal cisterns and subarachnoid space. The hypothesis that LD could be advantageous was first tested in the LUMAS trial [42], a monocentric RCT involving good-grade patients. While the primary findings showed a decrease in delayed ischemic neurological deficits at discharge, this did not translate to improved 6-month functional outcomes. One possible explanation is that the good-grade aSAH patients studied in LUMAS were at a lower risk for secondary complications, rendering the trial underpowered to detect significant differences. The EARLYDRAIN trial compared the addition of an LD placed within 48 h of rupture to standard-of-care alone, which included management with/without EVD, in 287 patients across all aSAH severity grades [41] (see Fig. 1). Controlled lumbar drainage of 5 ml/hour was performed for at least four days, starting the day after aneurysm treatment, regardless of the presence of hydrocephalus. The primary endpoint was the rate of poor outcome, defined as mRS scores of 3–6. In the LD group, poor outcomes were significantly lower, observed in 33% (47/144) patients compared to 45% (64/143) with a number-needed-to-treat of 8.3 to prevent an unfavorable outcome. Outcome improvement was paralleled by fewer secondary infarctions (29% in the LD group vs 40%); mortality was similar between groups. The treatment effect was consistent across subgroups. An updated systematic review and meta-analysis, including EARLYDRAIN data, support the effectiveness of lumbar CSF drainage in improving 6-month mortality following aSAH [97] with a key emphasis on the reduction of infarctions. Of note, none of the included studies reported a higher rate of fatal or non-fatal complications associated with LD use. The investigation of CSF filtration through lumbar catheters [98] is based on similar assumptions of the benefits of blood removal from CSF.

Further research should integrate ICP management when indicated and focus on drainage rate and duration of CSF diversion.

Seizures

Seizures occur at the time of aneurysm rupture in about 10% [99], more frequently in young, poor-grade aSAH patients with anterior circulation aneurysms, and have been associated with aneurysm rebleeding [100].

Following aneurysm treatment, clinical seizures are overall rare, with higher seizure risk after clipping [101, 102]; they are associated with unfavorable functional outcomes and development of epilepsy [103]. Electrographic seizures, detected through EEG monitoring, occur during the acute in-hospital course in about 17% of aSAH patients [101, 104]. Abnormal epileptiform activity can

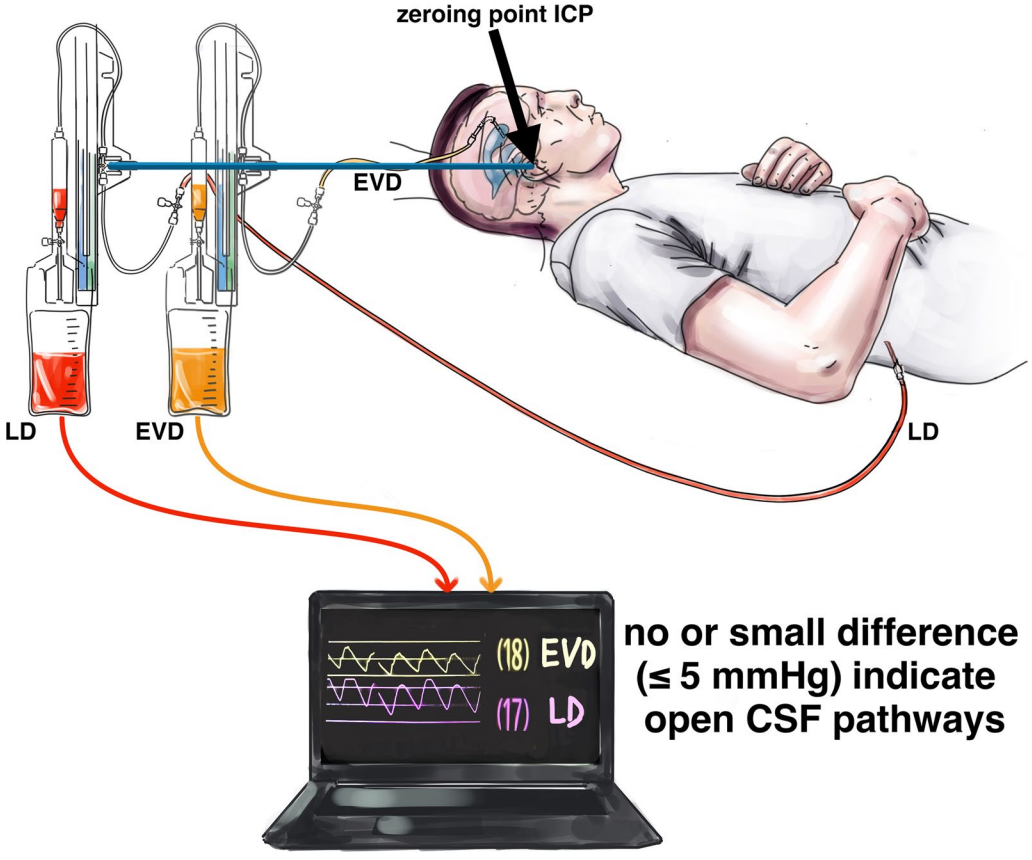


Fig. 1 Schematic of cerebrospinal fluid drainage systems in aSAH This figure illustrates the simultaneous use of EVD and LD systems for monitoring and draining CSF in patients with aSAH. The zeroing point for EVD and LD systems is marked near the level of the external auditory meatus [arrow], ensuring accurate pressure readings. A minimal pressure gradient (< 5 mmHg) between the two systems suggests patent CSF flow pathways. This approach is particularly relevant in cases of hydrocephalus or raised ICP, as it enables tailored interventions to prevent further complications. The figure also underscores the importance of precision in ICP monitoring, as it directly relates to optimizing CSF drainage strategies

be detected in up to two-thirds of patients, with a higher epileptiform burden in patients who develop DCI [105].

Despite the absence of clinical trials to guide treatment decisions, antiseizure medications (ASM) such as levetiracetam are frequently given until aneurysms are secured and the risk of rebleeding is minimized. Prophylaxis with ASM and treatment of these seizures, however, vary widely [106], and are highly controversial. The benefits of prolonged prophylaxis extending beyond the time of aneurysm treatment have not been established [107]. In these preliminary clinical trials, older medications such as phenytoin were associated with worse outcomes, and the benefits of newer agents such as levetiracetam may be limited to aSAH patients with evidence of EBI [107]. Practice in ASM prescription is variable, with higher rates of ASM for patients with higher grade SAH [106]. Guidelines support the treatment of seizures and status epilepticus for the first week after bleeding [13], but aggressive ASM treatment of other epileptiform discharges may not be beneficial [108]. Epilepsy may develop months or years after the bleeding, particularly in patients with premorbid disability, seizures within the first week after aSAH, surgical aneurysm treatment, poor admission neurological status, and larger volumes of subarachnoid and intraventricular blood [103].

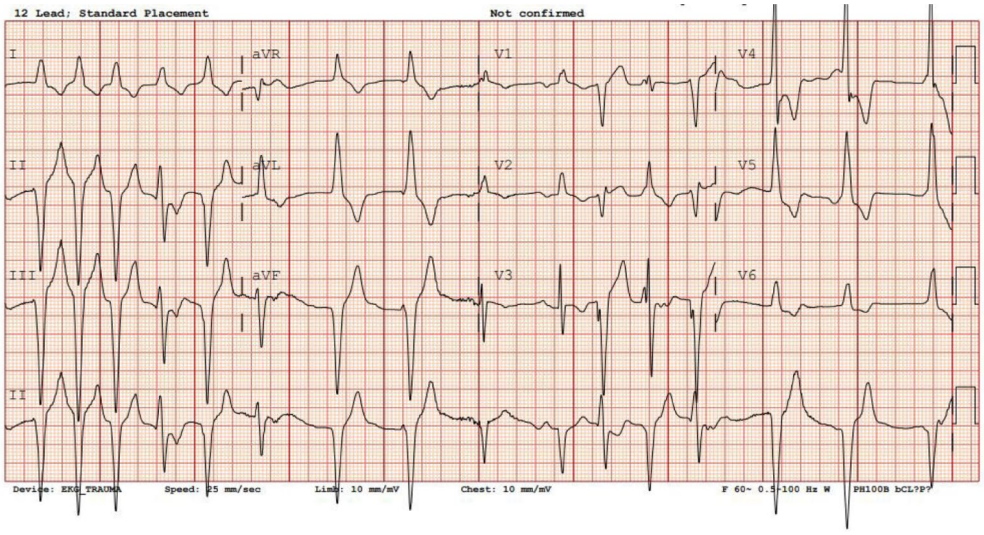
No conclusive data is guiding the current management approach. One published trial protocol compares valproate versus placebo in good-grade patients without seizures at presentation [109]. Future steps should focus on clarifying optimal indication, duration, and type of ASM and assessing the long-term impact of early epileptiform activity and seizure management on functional outcomes.

Large vessel vasospasm

Vasospasm, in a clinical context commonly defined as the narrowing of large and medium-sized intracranial arteries, although also occurring in microcirculation, results from a combination of endothelial dysfunction, smooth muscle cell hypercontractility, and, as emerging evidence suggests, profound extracellular matrix remodeling [110–112]. Typically manifesting 3–14 days after aSAH, vasospasm is angiographically evident in approximately 70% of patients, although less than half develop

A **Electrocardiographic changes**

- Most frequent cardiac complication; seen in up to 80%[1]
- Most common: ST depression, QT prolongation, and T-wave inversions



ECG with diffuse T-wave inversions that do not reflect an anatomic coronary territory ("cerebral T waves"), with tachyarrhythmia

B **Neurogenic left ventricular dysfunction**

- "Neurogenic cardiomyopathy", "Takotsubo" or "stress" cardiomyopathy
- Any degree of left ventricular dysfunction reported in up to 50%; severe heart failure in up to 4%
- Apical ballooning = classic manifestation; midventricular, basal, focal hypokinesia, or global hypokinesia can be seen
- Left ventricular dysfunction generally reversible with recovery over days to weeks
- Associated with poor outcomes after aneurysmal subarachnoid hemorrhage[2]

Transthoracic echocardiography (apical view) showing neurocardiogenic left ventricular (LV) dysfunction with apical ballooning (arrows) and markedly reduced ejection fraction of 30%

C **Differentiation between neurogenic and acute ischemic cardiac injury**[3]

Neurocardiogenic injury	Acute myocardial ischemia
Troponin I elevated in 20-40%; elevation range often low	Troponin elevation higher
Early peak of troponin elevation	Later peak of troponin elevation
ST elevations in precordial leads without reciprocal ST depression in inferior leads	ST-segment elevations in 2 contiguous leads with reciprocal ST-depression in inferior leads
QTc prolongation in absence of marked Q waves	Marked Q waves

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Fig. 2 (See legend on next page.)

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Fig. 2 Cardiac complications after aneurysmal subarachnoid hemorrhage Cardiac complications include neurocardiogenic myocardial injury, disturbance of left ventricular failure, arrhythmias and electrocardiographic changes. Figure 2 provides an overview of characteristics, observed rate and examples of a neurocardiogenic electrocardiographic (**A**) and echocardiographic finding with apical ballooning [arrows] (**B**), and a comparison between neurogenic and acute ischemic cardiac injury (**C**)

clinical deterioration due to DCI. Transcranial Doppler ultrasonography (TCD) monitoring is commonly utilized to detect large vessel vasospasm, albeit important caveats exist [113] Even though angiographic vasospasm increases the odds of cerebral infarction nearly ninefold, it is not a prerequisite for DCI, reflecting the complex and overlapping mechanisms underlying adverse outcomes [114].

An endogenous rise in blood pressure is frequently observed after aSAH and may serve as an early indicator of developing vasospasm [115] or cerebral hypoperfusion. In clinical practice, post-securement BP management varies widely [82]. Induced hypertension is commonly employed as the primary intervention for DCI—provided the patient's cardiac status is favorable [116]. However, optimal trigger thresholds and target blood pressure levels remain unclear [117]. Notably, the only randomized controlled trial evaluating induced hypertension was terminated early, and its limited sample size precluded drawing definitive conclusions regarding its benefit [118]. Despite these uncertainties, hemodynamic augmentation using agents such as norepinephrine and phenylephrine is widely practiced, while vasopressin is generally avoided given its association with significant hyponatremia [119, 120]. Current guidelines endorse a strategy of permissive autoregulation and blood pressure augmentation in patients with DCI, while cautioning against routine prophylactic hemodynamic manipulation due to iatrogenic risks [13]. Milrinone has been proposed as a vasodilator to counter vasospasm [121], and is increasingly adopted into practice, with a reduction of endovascular rescue therapies. Although inotropes have the potential to improve cerebral blood flow when autoregulation is impaired [119], their heterogeneous effects warrant further investigation, and existing data lack robust comparison in clinical trials.

Endovascular rescue therapy—comprising intra-arterial vasodilator infusion (with agents such as nimodipine, verapamil, nicardipine, or milrinone) and balloon angioplasty—remains an option when hemodynamic augmentation is either ineffective or contraindicated. A small phase 2 trial, however, reported worse outcomes with endovascular rescue compared to blood pressure augmentation [122]. While observational studies indicate frequent clinical use of endovascular strategies [116], their impact on long-term functional outcomes remains unproven [123]. Clazosentan, an endothelin-receptor antagonist with anti-vasospastic properties, showed promise in the prevention, reversal, and amelioration of vasospasm in phase 2 trials [124, 125], and was investigated in a phase 3 RCT [126] in which it did not lead to reduced DCI or improved outcomes. Intrathecal administration of nicardipine has shown promising results in the prevention of moderate-severe vasospasm [73], setting the basis for a phase 3 trial.

Finally, it is important to note that current data do not address hemodynamic management in patients undergoing treatment with newer devices, which may not achieve immediate aneurysm securement comparable to surgical clipping or endovascular coiling and thus may result in different cerebral hemodynamic changes [127].

Systemic complications

Cardiac complications

Cardiac injury after aSAH (see Fig. 2) is mediated through increased ICP, central autonomic dysfunction, catecholamine release, and inflammation with activation of cell-death pathways [128]. Neurocardiogenic dysfunction in the post-aSAH course has been well described and spans a wide range of arrhythmias, electrocardiographic changes, troponin elevation, wall motion abnormalities, and serious cardiac events, especially for patients with severe grades and high blood burden around the brainstem [129]. While myocardial injury is associated with mortality and poor neurological outcome [130], and hemodynamic manipulation for the treatment of DCI may increase the risk of further cardiac complications, a targeted approach to, or stratification according to cardiac abnormalities, has not been a focus of interventional trials thus far.

Pulmonary complications

Pulmonary complications after aSAH include typical ICU-pulmonary complications such as atelectasis, pneumonitis, and pneumonia, which result from impaired neurologic function and aspiration as well as inflammation over the course of the disease, (Table 2) and neurogenic pulmonary edema (NPE), which occurs in the setting of catecholamine toxicity [131]. Not only do these problems complicate management; they are associated with worse outcomes [132]. Recent advances, albeit only for intermediate outcomes, include bundle approaches and prevention of ventilator-associated pneumonia (see Table 2).

Despite the impact of pulmonary function on cerebral performance through modulation of cerebrovascular reactivity and vessel caliber, trials targeting the reduction

Table 2 Pulmonary complications after aneurysmal subarachnoid hemorrhage

Type of complication	Considerations
Hypoxemia	Important cause of secondary brain damage [133]
	Target 80–120 mmHg for arterial oxygen concentration [134]
	Consideration of additional neuromonitoring (cerebral oxygenation) to individualize optimal targets [134]
Hypocarbia	May lead to exacerbation of cerebral vasoconstriction → should be carefully titrated [135]
	Target 35–45 mmHg for arterial carbon dioxide concentration [134]
Hospital-acquired pneumonia	Bundle approach (including protective ventilation, early enteral nutrition, standardization of antibiosis) →ventilator-free days in patients with acute brain injury; no impact on mortality [136, 137]
Ventilator-associated pneumonia	Occurs in up to 22% of aSAH cases
	PROPHY-VAP (single early dose of ceftriaxone in ventilated brain-injured patients, including 40% with SAH) →decrease in pneumonia and mortality [138]
Acute respiratory distress syndrome (ARDS)	Occurs in up to 4% of patients with aSAH
	Observed frequency of ARDS has declined over time [139]
	Management with lung-protective ventilation, balancing with need for cerebral perfusion
Neurogenic pulmonary edema	Occurs in ~ 13% [140]
	Likely related to systemic catecholamine release similar to neurocardiac disturbances [141]
	Risk factors: female sex, poor neurologic status, elevated troponin, elevated white blood cell count, presence of ECG abnormalities
	Management: general supportive maneuvers, including use of positive end-expiratory pressure and avoidance of hypervolemia

aSAH, aneurysmal ssubarachnoid hemorrhage; ARDS, acute respiratory distress syndrome; SAH, subarachnoid hemorrhage

of DCI have not systematically incorporated these aspects.

Fever

Fever occurs in up to 70% of aSAH patients, with the highest burden between post-bleed days 5–10. Regardless of the etiology—i.e., neurogenic, infectious, or drug-related—, fever is associated with an increased risk of DCI, longer hospital stay, poor short- and long-term outcomes, and mortality [142, 143]. The pathophysiology for the impact of fever on outcomes is only partially understood and includes a link between elevated body temperature and secondary brain injury through increased cerebral metabolic demand, oxygen consumption, ICP, mitochondrial dysfunction, disruption of the blood–brain barrier, and CSD [5, 144]. While small observational studies reported attenuation of secondary brain injury by lowering the core temperature, the recent INTREPID RCT [145], investigating early fever prophylaxis after acute strokes, including aSAH, did not show an outcome benefit compared to standard-of-care which entailed fever management upon occurrence, despite a significant reduction of fever burden, and effectiveness of therapeutic temperature management during the acute phase of aSAH remains uncertain [13]. Further, achieving normothermia is challenging: Pharmacologic strategies, including acetaminophen or nonsteroidal anti-inflammatory drugs, are frequently ineffective [146], and cooling devices may trigger shivering and require more sedation. Importantly, although fever is consistently linked to poorer outcomes, treatment of fever has not been shown to improve outcomes. Despite this, a recommended consensus suggests continuously monitoring core temperature and treating temperatures ≥ 37.5 °C, targeting normothermia [147]. Brain temperature is rarely measured in practice, and the body of data on brain temperature remains limited; as such, brain temperature monitoring cannot generally be recommended, although core temperature is an imperfect proxy, differing from brain temperature by up to 2 °C.

Future research should include standardized definitions and reporting of fever episodes and focus on identifying optimal target temperature and effective management strategies, distinguishing preventive versus reactive fever control, and considering the etiology of fever.

Anemia

At least two of five patients with aSAH have or develop anemia, and anemia can be associated with worse outcomes, particularly if occurring during the course of disease [148]. Reduced oxygen delivery due to anemia may amplify secondary brain injury [149]. Current guidelines were published before the publication of two randomized trials, Subarachnoid Hemorrhage Red Cell Transfusion Strategies and Outcome (SAHARA) [150] and TRansfusion strategies in Acute brain INjured patients (TRAIN) [151], investigating transfusion strategies. SAHARA found no differences in neurologic outcomes between liberal (≥ 10 g/dL) and restrictive (≤ 8 g/dL) groups, while TRAIN, comparing transfusion thresholds of 7 g/dL versus 9 g/dL in a mix of acute brain injury including 23% SAH, found better 6-months outcomes for the higher hemoglobin group [151] including lower risk of cerebral ischemia (relative risk 0.63; 95% CI 0.41–0.97) in a secondary analysis focused on SAH patients [152]. While methodologically more robust, the a-priori-defined outcome difference detection of 25% in SAHARA, as well as the higher transfusion thresholds, may have prevented the detection of a favorable transfusion threshold as found in TRAIN. Meta-analyses weighing these differences are underway.

Electrolyte disturbances

Sodium disturbances after aSAH, including cerebral salt-wasting and hyponatremic natriuretic syndrome, and related available data on practice guidance are well described [153]. The assessment of risk factors for dysnatremia and its impact on outcomes has yielded conflicting results [153]. The relationship of sodium variability with DCI has also been inconsistent; the most recent data on the topic did not demonstrate sodium levels or fluctuations predictive of DCI, yet found higher sodium levels and fluctuations associated with poor 6-month outcomes independent of DCI [154]. Hypertonic saline or enteral sodium supplementation is often used to treat hyponatremia—especially severe hyponatremia (i.e., serum sodium level < 120 mmol/L) as this raises the risk of cerebral edema and seizures[155], while an optimal target or range for mild to moderate hyponatremia is much less clear. Fluid restriction should be avoided, as hypovolemia increases the risk of DCI. Both mineralo- and glucocorticoids may prevent hyponatremia but can trigger hyperglycemia and hypokalemia. Treating *established* hyponatremia with mineralocorticoids is not adequately studied. Guidelines summarize current evidence as insufficient to recommend on use of mineralocorticoids or other interventions to prevent or correct hyponatremia [12, 13]. A survey of current practice in the U.S. showed that while generally considered for use in 70% of sites, fludrocortisone is used in less than 25% of real-world practice[156].

Hypomagnesemia, detected in up to 50%, is associated with a higher risk of DCI. Although avoidance of hypomagnesemia is thus generally recommended, augmentation with intravenous magnesium sulfate has not improved outcomes in RCTs [157, 158]. A criticism of those trials is that treatment may have commenced too late; smaller subsequent studies continue to report better outcomes with variable protocols for magnesium sulfate infusions, supporting the utility of another look at this topic [159].

Long-term outcomes after aSAH

While most data to date indicate that fewer than one-third of survivors recover fully, there is a striking lack of long-term observational outcome data. At one follow-up, cognitive impairment is found in 71% [4], and even among patients with what is generally dichotomized as a "good functional outcome" (i.e., mRS of 0–2), nearly half show cognitive deficits [160]. A third develops a post-SAH syndrome with fatigue, and cognitive and emotional problems [161]. However, improvement can occur up to 4 years after onset, with good outcomes even in survivors with initially poor function [162]. Despite this recognition, structured inclusion of functional measurements of neuropsychological function [163] in aSAH trials is lacking [164].

Evidence gaps and clinical trials in aSAH

Major evidence gaps exist for the management of most post-securement complications encountered after aSAH. There are numerous ongoing and completed clinical trials for aSAH. The Clinical Trials.gov repository lists 25 completed trials over the past 20 years, and similar numbers of active phase 2–4 trials investigating pharmacologic or interventional innovations (see Table 3). However, despite numerous preclinical and pilot investigations, many subsequent trials in aSAH research are terminated, most commonly due to a lack of sufficient enrolment. Further, important aspects that have been identified and investigated for many years, for example, the impact of CSD on the development of DCI [165] and inflammation, have not moved forward to impactful clinical investigations. Additionally, the lack of a concerted approach to outcomes selection and measurements [166] limits data comparison and generalizability. While some of the evidence gaps will be addressed (Table 3), others are unlikely to be efficiently explored in the current landscape and may require an approach utilizing well-designed prospective cohorts, target trial emulation, clinical trials with bundles of care [167], comparative effectiveness or advanced causal inference methods with robust statistical adjustment and transparent reporting, and a trial platform allowing for overcoming challenges in SAH research [168].

Conclusions

aSAH remains a complex condition with multifaceted complications that significantly influence outcomes. While advancements in understanding pathophysiological mechanisms have refined early management strategies, many aspects lack high-quality evidence.

Future research should focus on targeted, individualized interventions and robust clinical trials to optimize treatment protocols for improved functional outcomes.

Methodology

Supporting the content of this review, a non-systematic search was performed on PubMed using the following search string ((((((((((((subarachnoid haemorrhage/hemorrhage) AND ((complications)) or (Rebleeding)) OR (lumbar drainage)) OR (intracranial pressure)) OR (Vasospasm)) OR (delayed cerebral ischemia)) OR (seizures)) OR (cardiac)) OR (pulmonary)) OR (Electrolytes)) OR (hormones)) OR (fever))) AND (("2019/01/01"[Date—Publication]:"3000"[Date—Publication])) Sort by: Most Recent.

Table 3. Current Pharmacotherapeutic and Interventional Clinical Trials in Aneurysmal Subarachnoid Hemorrhage*

	Name/Topic	Design	Expected participants	National Clinical Trial Identifying Number
Pharmacotherapeutic Trials				
Phase 2	LEVOSAH: Levosimendan (vs placebo)	Single-center RCT	30	NCT05664191
	ISCHEMIA: Nadroparine (vs standard LMWH)	Single-center RCT	100	NCT04507178
	Effect on intraoperative dexmedetomidine on incidence of vasospasm	Single-center RCT	90	NCT06352593
	OPTIMIL: milrinone to prevent DCI	Multicenter RCT	234	NCT04282629
	DISH: Deferoxamine vs placebo	Dual center RCT	120	NCT04566991
	DASH: Deferoxamine vs placebo	Dual center RCT	40	NCT02875262
	FLASH: fludrocortisone vs placebo	Multicenter RCT	524	NCT06409364
	CIAO@SAH: C1 Inhibitor Cinryze vs placebo	Dual center RCT	128	NCT06359782
	Xe-SAH: Xenon as neuroprotective agent	Multicenter RCT	160	NCT04696523
	HASH: albumin for optimal fluid management	Single-center RCT	84	NCT06548477
Phase 2–3	SXN-CVS: Shuxuening Injection for the Prevention of vasospasm	Single-center RCT	50	NCT06138353
Phase 3	STRIVE-ON: intravenous formulation of nimodipine	Multicenter RCT	100	NCT05995405
	FINISHER: Dexamethasone vs placebo	Multicenter RCT	334	NCT05132920
	Ue-STAR: Ultra-early statin (vs standard care)	Multicenter randomized trial	522	NCT06559072
	SCIL: Interleukin-1 Receptor Antagonist vs placebo	Multicenter RCT	612	NCT03249207
Phase 4	LD-ITUK: Lumbar drainage plus intrathecal urokinase	Multicenter RCT	424	NCT06284642
	iVAST: Intra-arterial Vasospasm Trial to determine the optimal intra-arterial drug treatment regimen for arterial lumen restoration post cerebral vasospasm	Multicenter randomized trial	330	NCT01996436

Interventional Trials

BLOCK-SAH: Pterygopalatine Fossa Block for Post-SAH Headache [169]. NCT06008795; multicenter RCT; n 195

BLOCK-CVS: Stellate Ganglion Block to prevent vasospasm [170]. NCT04691271; single center RCT; n 202

FAST-IT: Intrathecal nicardipine for vasospasm via EVD vs LD vs sham. NCT06329635; multicenter RCT; n 396

ASTIM-MT: Treatment Based on Intraventricular ICP Monitoring; NCT06288659; multicenter RCT; n 368

Impact of Early Mobilization on Outcome. NCT06436508; single center RCT; n 50

GES-aSAH: Gamma Entrainment Stimulation for Cognitive Dysfunction After aSAH. NCT06346015; single center randomized trial; n 60

Trials evaluating Remote Ischemic Conditioning in Aneurysmal SAH; three trials in China: NCT06032533, NCT06819657 & NCT06711302; two single center RCT (n 40 & 100, respectively), one multicenter (n = 500)

Early Versus Ultra Early Surgical Treatment of Ruptured Intracranial Aneurysms; NCT06457347; randomized trial; n 100

*as listed on Clinical Trials.Gov [accessed on 4/11/2025 for active, recruiting or not yet recruiting trials with study start between 1/1/2004 and 4/11/2025]. RCT, Randomized Controlled Trial; DCI, Delayed Cerebral Ischemia; n, number of (anticipated) participants; ICP, intracranial pressure

Glossary of terms/dictionary

aSAH: Aneurysmal Subarachnoid Hemorrhage	A type of haemorrhagic stroke caused by the rupture of an aneurysm in the subarachnoid space.
ASM: Antiseizure Medications	Medications used to prevent or control seizures by stabilizing neuronal activity.
BBB:	Blood brain barrier
CSD: Cortical Spreading Depolarizations	Waves of neuronal and glial depolarization followed by prolonged depression of brain activity, associated with ischemia and brain injury.
CSF: Cerebrospinal Fluid	The fluid that surrounds the brain and spinal cord, providing protection, nutrient delivery, and waste removal.

CTA: Computed Tomography-Angiography	An imaging technique that combines computed tomography with a contrast agent to visualize blood vessels in the brain and other areas.
CT-Perfusion (CTP):	A CT imaging technique that evaluates cerebral blood flow, volume, and transit time to detect ischemia or perfusion abnormalities.
cEEG: Continuous Electroencephalography	Continuous monitoring of brain electrical activity to detect abnormalities such as seizures or ischaemic patterns. The quantitative aspect involves the transformation of raw EEG waveforms into numerical data and visual trends, such as power spectra, alpha-delta ratios, and heatmaps, enabling easier detection of patterns like seizures, ischemia, or cortical slowing.
DCI: Delayed Cerebral Ischemia	A clinical syndrome occurring 4-14 days after subarachnoid hemorrhage, characterized by reduced blood flow leading to neurological deficits.
EBI: Early Brain Injury	Damage occurring within 72 hours after a subarachnoid hemorrhage, encompassing cellular and vascular mechanisms leading to brain dysfunction.
ECG:	electrocardiography.
EVD: External Ventricular Drainage	A medical procedure to drain excess CSF from the brain's ventricles to relieve pressure.
ICP: Intracranial Pressure	The pressure within the skull, influenced by brain tissue, cerebrospinal fluid, and blood volume, critical for maintaining normal cerebral function.
LD: Lumbar Drain	A device used to drain cerebrospinal fluid from the lumbar spine.
mRS: Modified Rankin Scale Score	A clinical scale used to measure the degree of disability or dependence in daily activities after a stroke.
NPE: Neurogenic Pulmonary Oedema	A form of acute pulmonary edema resulting from sympathetic overactivation following neurological injury, such as subarachnoid hemorrhage.
$PaCO_2$: Partial Pressure of Arterial Carbon Dioxide	The amount of carbon dioxide dissolved in arterial blood, reflecting respiratory function and metabolic balance.
PEEP: Positive End-Expiratory Pressure	A ventilatory setting used to maintain airway pressure above atmospheric levels to improve oxygenation and prevent alveolar collapse.
RCTs: Randomized Controlled Trials	A type of scientific experiment that randomly assigns participants to intervention or control groups to evaluate the efficacy of medical treatments.
SAH:	Subarachnoid Hemorrhage
SBP: Systolic Blood Pressure	The pressure exerted in arteries during the contraction of the heart, a vital parameter in monitoring cardiovascular health.
TCD: Transcranial Doppler Ultrasonography	A non-invasive ultrasound method to measure cerebral blood flow velocity in major brain arteries.

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